UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,283	02/02/2004	Michael P. Maher	AUROBIO.026D2D1	9653

20995 7590 03/30/2005

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
FERNANDEZ, SUSAN EMILY	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/771,283	MAHER ET AL.	
	Examiner	Art Unit	
	Susan E. Fernandez	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/19,8/23,4/30.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 are pending and are presented for examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. (WO 96/41166) in view of Brust-Mascher et al. (Biophysical Journal, 1998, 75(4): 1669-1678).

Tsien et al. discloses a screening method for identifying drugs that affect ion channel activity corresponding to changes in membrane potentials in cells (pages 42 and 43). The

invention comprises the steps of loading the cells with first and second reagents for measuring membrane potential (page 42, lines 31-33). The first reagent comprises a transmembrane potential redistribution dye, also described as a hydrophobic fluorescent ion capable of redistribution upon changes in membrane potential (page 3, lines 7-11). Furthermore, the transmembrane potential redistribution dye is considered an ion sensitive fluorescent molecule and an electrochromic transmembrane potential dye. The second reagent comprises a chromophore, preferably a fluorophore capable of FRET or electron transfer (page 3, lines 25-30). Thus the second reagent is considered a FRET based voltage sensor, an electrochromic transmembrane potential dye, or an ion sensitive fluorescent molecule. Additionally, Tsien et al. indicates that "the invention also includes the use of recombinant cells into which ion transporters, ion channels, pumps and exchangers have been inserted and expressed by genetic engineering" (page 44, lines 1-3). Finally, the Tsien invention includes exposing cells to a stimulus that modulates an ion channel (page 43, lines 4-8), and applying high throughput screening methods involving depositing cells into the wells of a microtiter plate (page 44, lines 12-22).

Tsien et al. does not expressly disclose the repetitive application of electric fields to cells in order to modulate the transmembrane potential of host cells.

Brust-Mascher et al. discloses the application of electric field pulses to fish keratocytes. The cells are loaded with indo-1-AM (page 1670, first column, fourth paragraph) which is an electrochromic transmembrane potential dye or an ion sensitive fluorescent molecule. Application of a single electric field pulse elicited calcium waves as a result of the stimulated calcium influx through the ion channels. More specifically, an electric field pulse causes a

voltage drop across the membrane of cells initially at a resting membrane potential prior to electrical stimulation. See page 1675, first column. Thus the transmembrane potential is set from a normal resting transmembrane potential to a transmembrane potential corresponding to calcium influx. Brust-Mascher et al. discloses the repetitive application of electric field pulses to cells wherein the cells remained electrotactic (page 1674, first column). Repeated pulse applications result in the ion channel cycling between a stimulated state (open channels) and an unstimulated state wherein the cells are oriented and migrated toward the cathode.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to practice the Tsien invention such that the host cells are stimulated by the repetitive application of electric field pulses.

One of ordinary skill in the art would have been motivated to do this because the repetitive application of electric field pulses would have allowed for small changes in the transmembrane potentials which Tsien et al. indicates is desirable for the practice of their invention. In particular, Tsien et al. states that "...methods and compositions are needed which are sensitive to small variations in transmembrane potentials and can respond both to rapid, preferably on a millisecond timescale, and sustained membrane potential changes" (page 2, lines 29-33). Furthermore, an electric field pulse serves as a stimulus that modulates an ion channel, thus fulfilling one of the Tsien invention step requirements. Thus a holding of obviousness is clearly required.

Claims 1-2 and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. and Brust-Mascher et al. as applied to claims 1-2 and 4-7 above, and further in view of Denyer et al. (Drug Discovery Today, 1998, 3(7): 323-332).

As discussed above, Tsien et al. and Brust-Mascher et al. render claims 1-2 and 4-7 obvious.

These references do not expressly disclose using cells comprising a radioactive ion as a voltage sensor.

Denyer et al. reviews high throughput screening (HTS) methods for voltage-gated ion channel modulators. Radiotracers, including radioactive ions, are noted for their use in tracing ion flux through ion channels (page 328). Furthermore, high throughput methods have been established for enabling ion channel assays with radiotracers.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have used radiotracers in addition to or in lieu of the voltage sensors disclosed in the Tsien invention.

One of ordinary skill in the art would have been motivated to do this because radiotracers and fluorescent-ion indicators "lend themselves to HTS in cell-based, 96-well formats" (page 327, first column). Furthermore, it would have been obvious to substitute art-accepted equivalents. Thus a holding of obviousness is clearly required.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. and Brust-Mascher et al. as applied to claims 1-2 and 4-7 above, and further in view of Tung et al. (Biophysical Journal, 1992, 63(2): 371-386).

As discussed above, Tsien et al. and Brust-Mascher et al. render claims 1-2 and 4-7 obvious.

These references do not expressly disclose repetitive application of biphasic electric fields.

Tung et al. discloses comparison of the effects of biphasic and monophasic electric fields on the electrical stimulation of cardiac cells (abstract). It was noted that "strength-duration curves derived from field stimulation show that over a wide range of pulse durations, biphasic waveforms can recruit and activate membrane patches about as effectively as can monophasic waveforms having the same total pulse duration" (abstract).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to practice the screening method with biphasic electric fields instead of monophasic electric fields.

One of ordinary skill in the art would have been motivated to make this substitution in order to have stimulated the cells with a reasonable expectation of success. A holding of obviousness is clearly required.

Claims 1-2, 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al. (Drug Discovery Today, 1999, 4(9): 431-439) in view of Tsien et al. (WO 96/41166).

Gonzalez et al. discloses a high throughput method for screening ion channel modulators. The disclosed high throughput method allows for "probing of various functional states" where electric fields are applied in combination with fast FRET probes for screening state-dependent blockers of sodium and potassium channels (page 437, second paragraph). More specifically, the

method consists of placing cells in microtiter plates wherein "...electrical stimulation can be used for rapid and repetitive stimulation..." in order to "rapidly activate channels that in turn induce membrane-potential changes" (page 437, first column, second paragraph). Thus, the transmembrane potential of the host cell is set to a stimulated state upon repetitive application of electric fields. When unstimulated, the transmembrane potential is a normal resting transmembrane potential. Since stimulation is repetitive, the ion channel of interest is cycled between the unstimulated voltage dependent state and the stimulated voltage dependent state. Moreover, the stimulated voltage dependent state corresponds to an opened channel state, where the ion channel of interest is released from inactivation.

Gonzalez et al. does not expressly disclose the expression of a target ion channel in a population of host cells.

Tsien et al. discloses a screening method for identifying drugs that affect ion channel activity corresponding to changes in the membrane potential (pages 42 and 43). Furthermore, Tsien et al. indicates that "the invention also includes the use of recombinant cells into which ion transporters, ion channels, pumps and exchangers have been inserted and expressed by genetic engineering" (page 44, lines 1-3).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have expressed a target ion channel in the host cells used in the screening methods of Gonzalez et al.

One of ordinary skill in the art would have been motivated to do this since it would have ensured that a specific target ion channel is present in the host cells involved in the assay described in Gonzalez et al. Furthermore, Tsien et al. and Gonzalez et al. share the common goal

of screening for ion channel modulators, thus one of ordinary skill in the art would have been motivated to have combined aspects of both. A holding of obviousness is clearly required.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al. and Tsien et al. as applied to claims 1-2 and 4-7 above, and further in view of Tung et al. (Biophysical Journal, 1992, 63(2): 371-386).

As discussed above, Gonzalez et al. and Tsien et al. render claims 1-2 and 4-7 obvious.

These references do not expressly disclose repetitive application of biphasic electric fields.

Tung et al. discloses comparison of the effects of biphasic and monophasic electric fields on the electrical stimulation of cardiac cells (abstract). It was noted that "strength-duration curves derived from field stimulation show that over a wide range of pulse durations, biphasic waveforms can recruit and activate membrane patches about as effectively as can monophasic waveforms having the same total pulse duration" (abstract).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to practice the screening method with biphasic electric fields instead of monophasic electric fields.

One of ordinary skill in the art would have been motivated to make this substitution in order to stimulate the cells by affecting membrane potentials with a reasonable expectation of success. A holding of obviousness is clearly required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan E. Fernandez whose telephone number is (571) 272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan E. Fernandez
Art Unit 1651
Assistant Examiner

sef

FRANCISCO PRATS
PRIMARY EXAMINER